A B C D

kDa
97
66
45

Figure 1

MRGPAVLLTV ALATLLAPGA GAPVQSQGSQ NKLLLVSFDG FRWNYDQDVD TPNLDAMARD GVKARYMTPA FVTMTSPCHF TLVTGKYIEN HGVVHNMYYN TTSKVKLPYH ATLGIQRWWD NGSVPIWITA QRQGLRAGSF FYPGGNVTYQ GVAVTRSRKE GIAHNYKNET EWRANIDTVM AWFTEEDLDL VTLYFGEPDS TGHRYGPESP ERREMVRQVD RTVGYLRESI ARNHLTDRLN LIITSDHGMT TVDKRAGDLV EFHKFPNFTF RDIEFELLDY GPNGMLLPKE GRLEKVYDAL KDAHPKLHVY KKEAFPEAFH YANNPRVTPL LMYSDLGYVI HGRINVQFNN GEHGFDNKDM DMKTIFRAVG PSFRAGLEVE PFESVHVYEL MCRLLGIVPE ANDGHLATLL PMLHTESALP PDALLVADGP CLPSLSQAKG CMPLSPAAPT PAWLLWCW

Figure 2

3/14 GTCCATCTGGAAGGCCCAGCATGAGAGGCCCGGCCGTCCTCACTGTGGCTCTGGCCACGCTCCTGGCTCCCGGGG MRGPAVLLTVALATLLAPGA CCGGAGCACCGGTACAAAGTCAGGGCTCCCAGAACAAGCTGCTCCTGGTGTCCTTCGACGGCTTCCGCTGGAACTACG G A P V Q S Q G S Q N K L L V S F D G F R W N Y D ACCAGGACGTGGACACCCCCAACCTGGACGCCATGGCCCGAGACGGGGTGAAGGCACGCTACATGACCCCCGCCTTTG Q D V D T P N L D A M A R D G V K A R Y M T P A F V TCACCATGACCAGCCCCTGCCACTTCACCCTGGTCACCGGCAAATATATCGAGAACCACGGGGTGGTTCACAACATGT T M T S P C H F T L V T G K Y I E N H G V V H N M Y ACTACAACACCACCAGCAAGGTGAAGCTGCCCTACCACGCCACGCTGGGCATCCAGAGGTGGTGGGACAACGGCAGCG YNTTSKVKLPYHATLGIQRWWDNGSV PIWITAQRQGLRAGSFFYPGGNVTYQ AAGGGGTGGCTGTGACGCGGAGCCGGAAAGAAGGCATCGCACACAACTACAAAAATGAGACGGAGTGGAGAGCGAACA G V A V T R S R K E G I A H N Y K N E T E W R A N I TCGACACAGTGATGGCGTGGTTCACAGAGGAGGACCTGGATCTGGTCACACTCTACTTCGGGGAGCCGGACTCCACGG D T V M A W F T E E D L D L V T L Y F G E P D S T G R E AGAGCATCGCGCGCAACCACCTCACAGACCGCCTCAACCTGATCATCACATCCGACCACGGCATGACGACCGTGGACA DRLNLIITSDHGM SIARNHLT

**WO** 2004/094629

PCT/SE2004/000628

Figure 3a

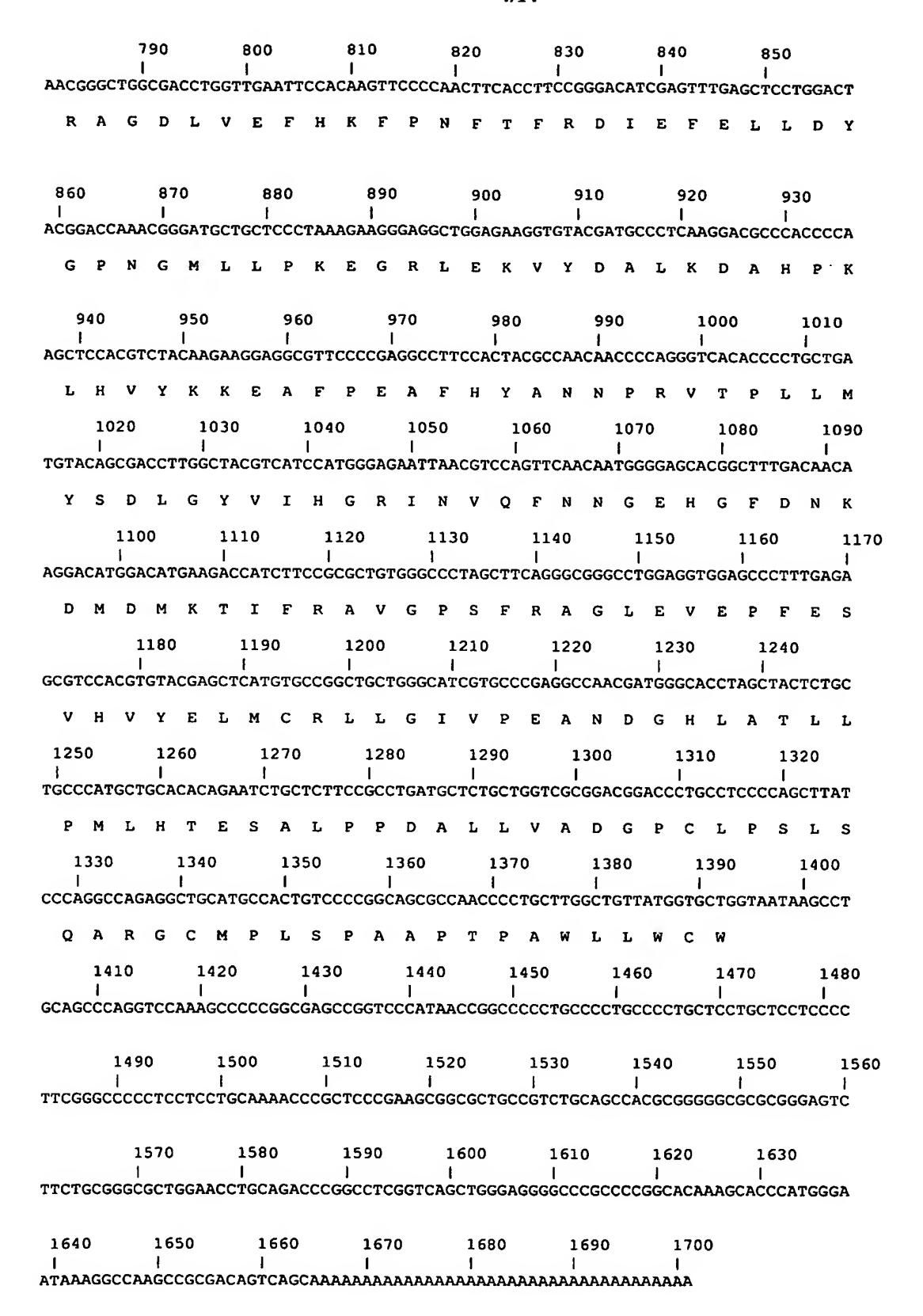
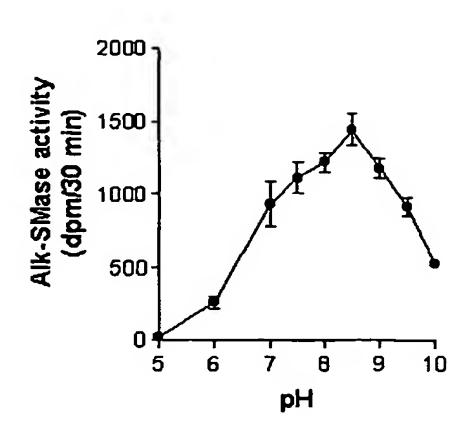


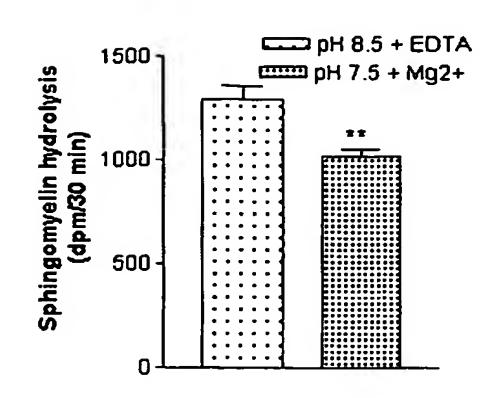
Figure 3b

B.

A.

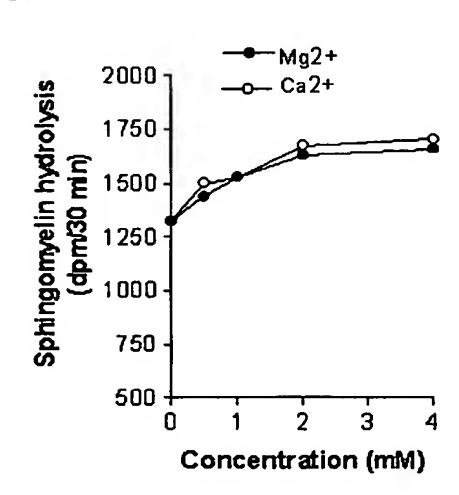






C.





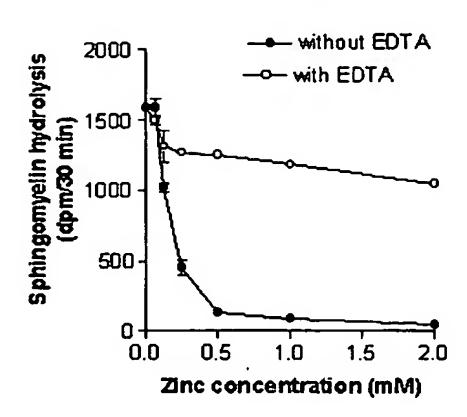


Figure 4

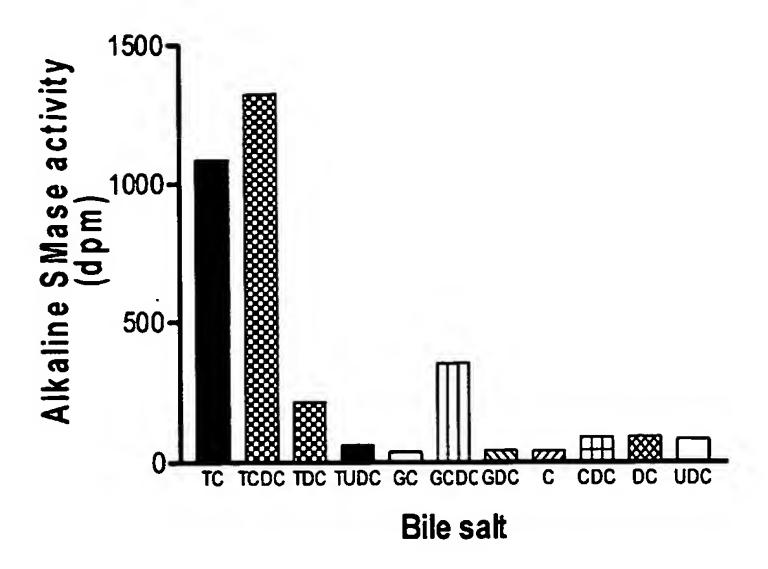


Figure 5

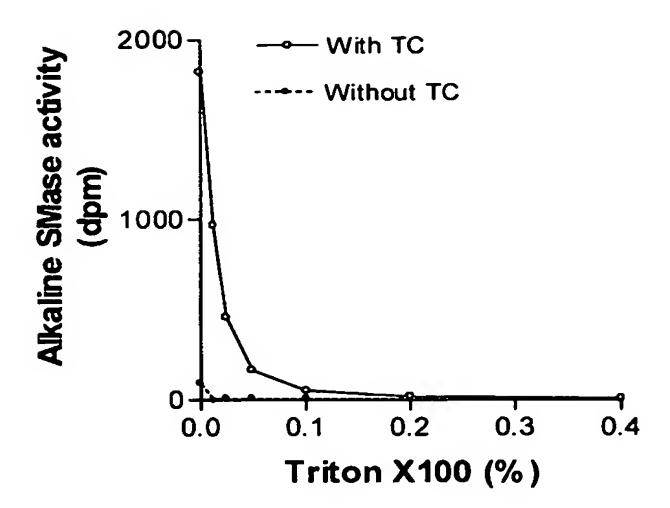


Figure 6

Sphingomyelin (ug)

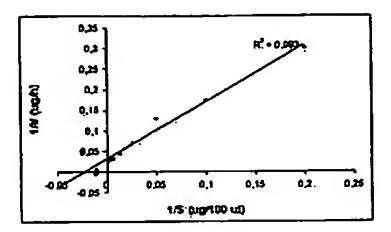


Figure 7

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CTATTTAGGT GACACTATAG AACAAGTTTG TACAAAAAG CAGGCTGGTA CCGGTCCGGA ATTCCCGGGA TGTCCATCTG GAAGGCCCAG CATGAGAGGC CCGGCCGTCC TCCTCACTGT GGCTCTGGCC ACGCTCCTGG CTCCCGGGGC CGGAGCACCG GTACAAAGTC AGGGCTCCCA GAACAAGCTG CTCCTGGTGT CCTTCGACGG CTTCCGCTGG AACTACGACC AGGACGTGGA CACCCCCAAC CTGGACGCCA TGGCCCGAGA CGGGGTGAAG GCACGCTACA TGACCCCCGC CTTTGTCACC ATGACCAGCC CCTGCCACTT CACCCTGGTC ACCGGCAAAT ATATCGAGAA CCACGGGGTG GTTCACAACA TGTACTACAA CACCACCAGC AAGGTGAAGC TGCCCTACCA CGCCACGCTG GGCATCCAGA GGTGGTGGGA CAACGGCAGC GTGCCCATCT GGATCACAGC CCAGAGGCAG GGCCTGAGGG CTGGCTCCTT CTTCTACCCG GGCGGGAACG TCACCTACCA AGGGGTGGCT GTGACGCGGA GCCGGAAAGA AGGCATCGCA CACAACTACA AAAATGAGAC GGAGTGGAGA GCGAACATCG ACACAGTGAT GGCGTGGTTC ACAGAGGAGG ACCTGGATCT GGTCACACTC TACTTCGGGG AGCCGGACTC CACGGGCCAC AGGTACGGCC CCGAGTCCCC GGAGAGGAGG GAGATGGTGC GGCAGGTGGA CCGGACCGTG GGCTACCTCC GGGAGAGCAT CGCGCGCAAC CACCTCACAG ACCGCCTCAA CCTGATCATC ACATCCGACC ACGGCATGAC GACCGTGGAC AAACGGGCTG GCGACCTGGT TGAATTCCAC AAGTTCCCCA ACTTCACCTT CCGGGACATC GAGTTTGAGC TCCTGGACTA CGGACCAAAC GGGATGCTGC TCCCTAAAGA AGGGAGGCTG GAGAAGGTGT ACGATGCCCT CAAGGACGCC CACCCCAAGC TCCACGTCTA CAAGAAGGAG GCGTTCCCG AGGCCTTCCA CTACGCCAAC AACCCCAGGG TCACACCCCT GCTGATGTAC AGCGACCTTG GCTACGTCAT CCATGGGAGA ATTAACGTCC AGTTCAACAA TGGGGAGCAC GGCTTTGACA ACAAGGACAT GGACATGAAG ACCATCTTCC GCGCTGTGGG CCCTAGCTTC AGGGCGGCC TGGAGGTGGA GCCCTTTGAG AGCGTCCACG TGTACGAGCT CATGTGCCGG CTGCTGGGCA TCGTGCCCGA GGCCAACGAT GGGCACCTAG CTACTCTGCT GCCCATGCTG CACACAGAAT CTGCTCTTCC GCCTGATGCT CTGCTGGTCG CGGACGGACC CTGCCTCCCC AGCTTATCCC AGGCCAAAGG CTGCATGCCA CTGTCCCCGG CAGCGCCAAC CCCTGCTTGG CTGTTATGGT GCTGGTAATA AGCCTGCAGC CCAGGTCCAA AGCCCCCGGC GAGCCGGTCC CATAACCGGC CCCCTGCCC TGCCCCTGCT CCTGCTCCTC CCCTTCGGGC CCCCTCCTCC TGCAAAACCC GCTCCCGAAG CGGCGCTGCC GTCTGCAGCC ACGCGGGGGC GCGCGGGAGT CTTCTGCGGG CGCTGGAACC TGCAGACCCG GCCTCGGTCA GCTGGGAGGG GCCCGCCCCG GCACAAGCA AAAAAAAAA AAAAAAAAA AGGGCGGCCG CTCTAGAGTA TCCCTCGAGG GGCCCAAGCT TACGCGTACC CAGCTTTCTT GTACAAAGTG GTCCCTATAG TGAGTCGTAT TATAAGCTAG GCA

Figure 8

**WO 2004/094629** 10/14 -----MRGPAVLLTVALATLLAPGAGAPVQSQGSQNKLLLVSFEGFRWNYDQD--VDT 51 Alk-SMase KGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLEGFRAEYLHTWGGLL 232 NPP1 HUMAN RGDCCTNYQVVCKGESHWVDDDCEEIKAAECPAGFVRPPLIIFSVDGFRASYMKKGSKVM 186 NPP2 HUMAN KKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFDLPPVILFSMCGFRAEYLYTWDTLM 181 NPP3 HUMAN NPP4 HUMAN -----KLLLVILLFSGLITGFRSDSSSSLPP-----KLLLVSFLGFRADYLKN--YEF 46 NPP5 HUMAN -----MTSKFLLVSFILAALSLSTTFSLQPD---QQKVLLVSFPGFRWDYLYK--VPT 48 Alk-SMase PNLDAMARDGVKARYMTPAFVTMTSPCHFTLVTGKYIENHGVVHNMYYNTTSKVKLPYHA 111 PVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMYDPKMNASFSLKS 292 NPP1 HUMAN NPP2 HUMAN PNIEKLRSCGTHSPYMRPVYPTKTFPNLYTLATGLYPESHGIVGNSMYDPVFDATFHLRG 246 NPP3 HUMAN PNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIIDNNMYDVNLNKNFSLSS 241 NPP4 HUMAN PHLQNFIKEGVLVEHVKNVFITKTFPNHYSIVTGLYEESHGIVANSMYDAVTKKHFS--D 104 NPP5\_HUMAN PHFHYIMKYGVHVKQVTNVFITKTYPNHYTLVTGLFAENHGIVANDMFDPIRNKSFSLDH 108 Alk-SMase TLGIQRWWDNGSVPIWITAQR-QGLRAGSFFYPGGNVTYQGVAVTRSRKEGIAHNYKNET 170 NPP1 HUMAN KEKFNPEWYKGE-PIWVTAKY-QGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEER- 349 REKFNHRWWGGQ-PLWITATK-QGVKAGTFFWS------VVIPHERR- 285 NPP2 HUMAN

NPP3 HUMAN KEQNNPAWWHGQ-PMWLTAMY-QGLKAATYFWPGSEVAINGSFPSIYMPYNGSVPFEER- 298 SNDRDPFWWNEAVPIWVTNQLQENRSSAAAMWPGTDVPIHDTISSYFMNYNSSVSFEER- 163 NPP4 HUMAN NPP5 HUMAN MNIYDSKFWEEATPIWITNQR-AGHTSGAAMWPGTDVKIHKRFPTHYMPYNESVSFEDR- 166 EWRANIDTVMAWFTEEDLDLVTLYFGEP到STG器RYGP-ESPERREMVRQVDRTVGYLRES 229 Alk-SMase --ILAVLQWLQLPKDERPHFYTLYLEEPESSGESYGP-VSSEVIKALQRVDGMVGMLMDG 406 NPP1 HUMAN

NPP2 HUMAN --ILTILQWLTLPDHERPSVYAFYSEQPAFSGHKYGP-FGPEMTNPLREIDKIVGQLMDG 342 -- ISTLLKWLDLPKAERPRFYTMYFEEPDSSGRAGGP-VSARVIKALQVVDHAFGMLMEG 355 NPP3 HUMAN NPP4 HUMAN --LNNITMWLNN-SNPPVTFATLYWEEPDASGRKYGPEDKENMSRVLKKIDDLIGDLVOR 220 NPP5\_HUMAN --VAKIIEWFT--SKEPINLGLLYWEDPEDMGHLGP-DSPLMGPVISDIDKKLGYLIQM 221 Alk-SMase

IARNHLTDRLNLIITS DEGMTTVDKRAGDLVEFHKFPNFTFRDIEFELLDYGPNGMLLP- 288 LKELNLHRCLNLILIS HGMEQGSCKK-----YIYLNKYLGDVKNIKVIYGPAARLRPS 460 NPP1 HUMAN LKQLKLHRCVNVIFVGDHGMEDVTCDR----TEFLSNYLTNVDDITLVPGTLGRIR-- 394 NPP2 HUMAN NPP3\_HUMAN LKQRNLHNCVNIILLADKGMDQTYCNK-----MEYMTDYFPRINFFYMYEGPAPRIRAH 409 NPP4 HUMAN LKMLGLWENLNVIITSDHGMTQCSQDR-----LINLDSCIDHSYYTLIDLSPVAAILP- 273 NPP5 HUMAN LKKAKLWNTLNLIITSDHGMTQCSEER-----LIELDQYLDKDHYTLIDQSPVAAILP- 274

Alk-SMase -----KEGRLEKVYDALKDAHP--KLHVYKKEAFPEAFHYANNPRVTPLLMYSDLGYVI 340 NPP1 HUMAN DVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQL 520 NPP2 HUMAN SKFSNNAKYDPKAIIANLTCKKPDQHFKPYLKQHLPKRLHYANNRRIEDIHLLVERRWHV 454 NPP3 HUMAN NIPHDFFSFNSEEIVRNLSCRKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLA 469 NPP4 HUMAN -----KINR-TEVYNKLKNCSP--HMNVYLKEDIPNRFYYQHNDRIQPIILVADEGWTI 324 NPP5 HUMAN -----KEGKFDEVYEALTHAHP--NLTVYKKEDVPERWHYKYNSRIQPIIAVADEGWHI 326 HGR-----INVQFNNGE GFDNKDMDMKTIFRAVGPSFRAGLEVEPFESVHVYELMC 392 Alk-SMase

ALN-----PSERKYCGSGF GSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMC 574 NPP1 HUMAN ARKPLDVYKKPSGKCFFQGD GFDNKVNSMQTVFVGYGPTFKYKTKVPPFENIELYNVMC 514 NPP2 HUMAN VRS-----KSN-TNCGGGNHGYNNEFRSMEAIFLAHGPSFKEKTEVEPFENIEVYNLMC 522 NPP3 HUMAN NPP4 HUMAN VLN-----ESS-QKLGDHGYDNSLPSMHPFLAAHGPAFHKGYKHSTINIVDIYPMMC 375 LQN-----KSDDFLLGNHGYDNALADMHPIFLAHGPAFRKNFSKEAMNSTDLYPLLC 378 NPP5 HUMAN

Alk-SMase RLLGIVPEANDGHLATLLPMLHT----- 415 NPP1 HUMAN DLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTR-NPRDNLGCSCN--PS 631 NPP2 HUMAN DLLGLKPAPNNGTHGSLNHLLRTNTFRPTMPEEVTRPNYPGIMYLQSDFDLGCTCD---D 571 NPP3 HUMAN DLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFANPLPTESLDCFCPHLQN 582 NPP4 HUMAN HILGLKPHPNNGTFGHTKCLL------ 405 NPP5\_HUMAN HLLNITAMPHNGSFWNVQDLLNSAMPRVVPYTQSTILLPG----- 418

------ESALPPDALLVADGPC 431 Alk-SMase NPP1 HUMAN ILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPL 691 NPP2 HUMAN KVEPKNKLDELNKRLHTKGSTEERHLLYGRPAVLYR-TRYDILYHTDFESGYSEIFLMPL 630 NPP3 HUMAN STQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSGFGKAMRMPM 642 NPP4\_HUMAN ----EAIAIVIGSLLVLTMLTCLIIIM 428 NPP5\_HUMAN -----SVKPAEYDQEGSYPYFIGVSLGSIIVIVFFVIF 451

Alk-SMase LPSLSQAKGCMPLSPAAPTPAWLLWCW------ 458 NPP1 HUMAN WTSYTVDRNDSFS--TEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNS 749 NPP2 HUMAN WTSYTVSKQAEVSSVPDHLTSCVRPDVRVSPSFSQNCLAYKNDKQMSYGFLFPPYLSSSP 690 NPP3 HUMAN WSSYTVPQLGDTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRTS 702 NPP4 HUMAN QNRLSVPRPFSRLQLQEDDDDPLIG------ 453 NPP5\_HUMAN IKHLIHSQIPALQDMHAEIAQPLLQA------ 477

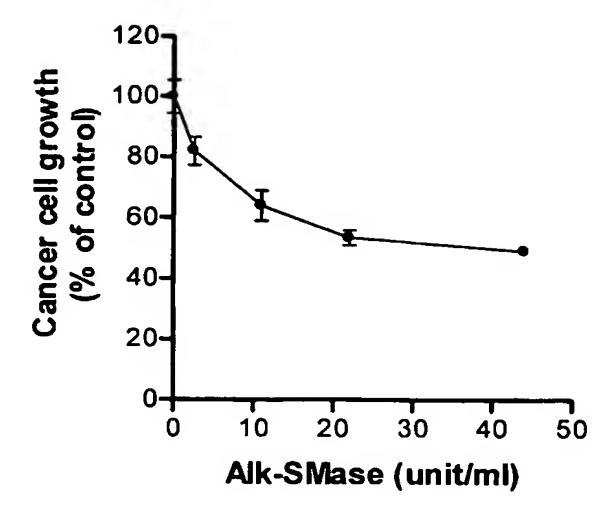


Figure 10

MRGPAVLLTV ALATLLAPGA GAPVQSQGSQ NKLLLVSFDG FRWNYDQDVD TPNLDAMARD 60
GVKARYMTPA FVTMTSPCHF TLVTGKYIEN HGVVHNMYYN TTSKVKLPYH ATLGIQRWWD 120
NGSVPIWITA QRQGLRAGSF FYPGGNVTYQ GVAVTRSRKE GIAHNYKNET EWRANIDTVM 180
AWFTEEDLDL VTLYFGEPDS TGHRYGPESP ERREMVRQVD RTVGYLRESI ARNHLTDRLN 240
LIITSDHGMT TVDKRAGDLV EFHKFPNFTF RDIEFELLDY GPNGMLLPKE GRLEKVYDAL 300
KDAHPKLHVY KKEAFPEAFH YANNPRVTPL LMYSDLGYVI HGRINVQFNN GEHGFDNKDM 360
DMKTIFRAVG PSFRAGLEVE PFESVHVYEL MCRLLGIVPE ANDGHLATLL PMLHTESALP 420
PDGRPTLLPK GRSALPPSSR PLLVMGLLGT VILLSEVA 458

Figure 11

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GTCCATCTGG AAGGCCCAGC ATGAGAGGCC CGGCCGTCCT CCTCACTGTG 50 GCTCTGGCCA CGCTCCTGGC TCCCGGGGCC GGAGCACCGG TACAAAGTCA 100 GGGCTCCCAG AACAAGCTGC TCCTGGTGTC CTTCGACGGC TTCCGCTGGA 150 ACTACGACCA GGACGTGGAC ACCCCCAACC TGGACGCCAT GGCCCGAGAC 200 GGGGTGAAGG CACGCTACAT GACCCCCGCC TTTGTCACCA TGACCAGCCC 250 CTGCCACTTC ACCCTGGTCA CCGGCAAATA TATCGAGAAC CACGGGGTGG 300 TTCACAACAT GTACTACAAC ACCACCAGCA AGGTGAAGCT GCCCTACCAC 350 GCCACGCTGG GCATCCAGAG GTGGTGGGAC AACGGCAGCG TGCCCATCTG 400 GATCACAGCC CAGAGGCAGG GCCTGAGGGC TGGCTCCTTC TTCTACCCGG 450 GCGGGAACGT CACCTACCAA GGGGTGGCTG TGACGCGGAG CCGGAAAGAA 500 GGCATCGCAC ACAACTACAA AAATGAGACG GAGTGGAGAG CGAACATCGA 550 CACAGTGATG GCGTGGTTCA CAGAGGAGGA CCTGGATCTG GTCACACTCT 600 ACTTCGGGGA GCCGGACTCC ACGGGCCACA GGTACGGCCC CGAGTCCCCG 650 GAGAGGAGGG AGATGGTGCG GCAGGTGGAC CGGACCGTGG GCTACCTCCG 700 GGAGAGCATC GCGCGCAACC ACCTCACAGA CCGCCTCAAC CTGATCATCA 750 CATCCGACCA CGGCATGACG ACCGTGGACA AACGGGCTGG CGACCTGGTT 800 GAATTCCACA AGTTCCCCAA CTTCACCTTC CGGGACATCG AGTTTGAGCT 850 CCTGGACTAC GGACCAAACG GGATGCTGCT CCCTAAAGAA GGGAGGCTGG 900 AGAANGTGTA CGATGCCCTC AAGGACGCCC ACCCCAAGCT CCACGTCTAC 950 AAGAAGGAGG CGTTCCCCGA GGCCTTCCAC TACGCCAACA ACCCCAGGGT 1000 CACACCCCTG CTGATGTACA GCGACCTTGG CTACGTCATC CATGGGAGAA 1050 TTAACGTCCA GTTCAACAAT GGGGAGCACG GCTTTGACAA CAAGGACATG 1100 GACATGAAGA CCATCTTCCG CGCTGTGGGC CCTAGCTTCA GGGCGGGCCT 1150 GGAGGTGGAG CCCTTTGAGA GCGTCCACGT GTACGAGCTC ATGTGCCGGC 1200 TGCTGGGCAT CGTGCCCGAG GCCAACGATG GGCACCTAGC TACTCTGCTG 1250 CCCATGCTGC ACACAGAATC TGCTCTTCCG CCTGATGGAA GGCCTACTCT 1300 CCTGCCCAAG GGAAGATCTG CTCTCCCGCC CAGCAGCAGG CCCCTCCTCG 1350 TGATGGGACT GCTGGGGACC GTGATTCTTC TGTCTGAGGT CGCATAACGC 1400 CCCATGGCTC AAGGAAGCCG CCGGGAGCTG CCCGCAGGCC CTGGGCCGGC 1450 TGTCTCGCTG CGATGCTCTG CTGGTCGCGG ACGGACCCTG CCTCCCCAGC 1500 TTATCCCAGG CCAGAGGCTG CATGCCACTG TCCCCGGCAG CGCCAACCCC 1550 TGCTTGGCTG TTATGGTGCT GGTAATAAGC CTCGCAGCCC AGGTCCAGAG 1600 CCCCCGGCGA GCCGGTCCCA TAACCGGCCC CCTGCCCCTG CCCCTGCTCC 1650 TGCTCCTCCC CTTCGGGCCC CCTCCTCCTG CAAAACCCGC TCCCGAAGCG 1700 GCGCTGCCGT CTGCAGCCAC GCGGGGGCGC GCGGGAGCTC TGCGGGCGCT 1750 GGAACCTGCA GACCCGGCCT CGGTCAGCTG GGAGGGGCCC GCCCCGGCAC 1800 AAAGCACCCA TGGGAATAAA GGCCAAGCCG CGACAGTCAG CAAAAAAAA 1841 AAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

Figure 12

14/14

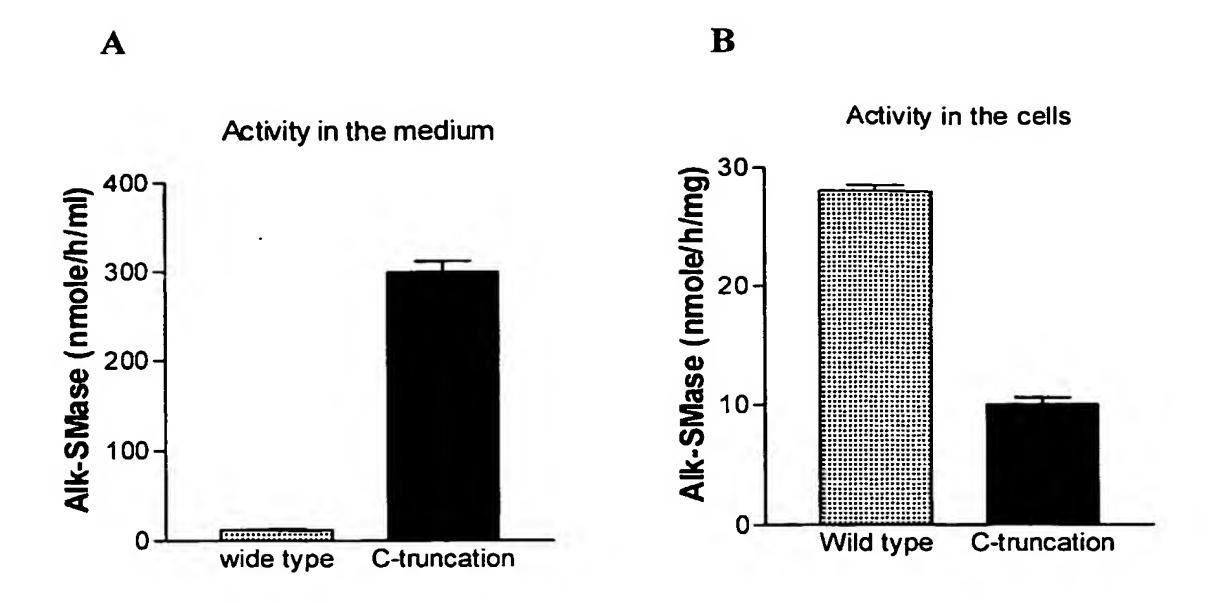


Figure 13